UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Date: September 23, 2004

Subject: Similarity of Linear Alkylbenzene Sulfonates and Alcohol Sulfates to Sulfonated Oleic Acid with Respect to Toxicity
Barcode: D308387

FROM: Timothy F. McMahon, Ph.D.
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This memorandum addresses data cited by the Registrant Johnson Diversey in support of the RED for sulfonated oleic acid and issues raised with respect to the bridging of toxicity data from linear alkylbenzene sulfonates and alcohol sulfates to sulfonated oleic acid.

In conclusion, the Agency believes that there are insufficient information at this time to bridge the toxicity data for linear alkylbenzene sulfonates and alcohol sulfates to the oleic acid sulfonates and its sodium salt. At a minimum, a mutagenicity battery (bacterial reverse mutation assay, in vitro mammalian gene mutation, and in vivo cytogenetics study), a 90-day oral rat study, and an oral developmental toxicity study would be required for oleic acid, sulfonated, sodium salt to demonstrate that these chemicals are toxicologically similar.

Background:

Oleic acid, sulfonated, sodium salt, is a pesticidal active ingredient currently being reassessed as part of reregistration. There are very few toxicity data available for this chemical, which are limited to acute toxicity data (acute oral, dermal, and inhalation studies and dermal irritation, and eye irritation studies). These data indicate low acute toxicity and that sulfonated oleic acid, sodium salt is a dermal and eye irritant.

On February 25, 2003, the Antimicrobials Division's Toxicity Endpoint Selection Committee (ADTC) met to discuss toxicology data for sulfonated oleic acid and discussed endpoint selection for use as appropriate in occupational/residential exposure risk assessments. This meeting was held as part of the development of the risk assessment for the Reregistration Eligibility Decision for sulfonated oleic acid.

At the ADTC meeting, the committee concluded that sulfonated oleic acid was related to oleic acid itself, a fatty acid that has been determined to be of low toxicity by OPP's Low Risk Focus Group and that has received food additive clearances by the Food and Drug Administration (FDA) without limitation, supporting the low toxicity of this chemical. Therefore, there is no risk of concern from the uses of sulfonated oleic acid as an antimicrobial pesticidal active ingredient (as an indirect food-contact sanitizer in milking equipment, food processing, handling, and storage areas, breweries, milk processing plants, meat processing plants, and beverage processing plants), and no toxicity endpoints are needed.

Registrant Submission:

Recently, a submission was made by one of the registrants supporting sulfonated oleic acid (Johnson Diversey 2004), in which it was stated that "the acute and chronic toxicity of [sulfonated oleic acid] is expected to be similar to that of other anionic surfactants." Specifically, the registrant states that "We believe that the overall toxicity of [sulfonated oleic acid] will be similar to that of both the alcohol sulfates and linear alkyl benzene. [Sulfonated oleic acid] is structurally similar to both the alcohol sulfates and linear alkyl benzene and is likely metabolized and excreted by similar mechanisms. Additional testing to further characterize the toxicity of oleic acid sulfonate is not necessary."

The OPP has no formal toxicology studies for sulfonated oleic acid (except the acute toxicity studies) but initially relied on the similarity of this chemical to oleic acid itself, which has shown a low order of toxicity from available data, analysis by the Low Risk Focus Group in OPP, and existing food additive clearances by the FDA. However, data are presented in the Human and Environmental Risk Assessment (HERA) documents that the registrant claims can be used to support the hazard of sulfonated oleic acid (available at www.heraproject.com). A summary is presented for both, taken from the HERA assessments.

Linear Alkylbenzene Sulfonates

Acute toxicity data for the linear alkylbenzene sulfonates (LAS) show a low order of toxicity for acute oral toxicity (LD_{50} values from 1086-1980 mg/kg) and dermal toxicity (LD_{50} of > 2000 mg/kg), some skin irritation potential (moderately irritating at 5%) and significant eye irritation using a 47% solution, non-irritating at 1%, and no dermal sensitization potential. Acute inhalation data are inconclusive but showed no effect up to 260 mg/m^3 (HERA 2004).

Non-acute testing shows effects on the liver and kidney, as summarized from the report below:

Summary of Repeated Dose Toxicity Studies for Linear Alkylbenzene Sulfonate

Table 23: Summary of the repeated dose toxicity tests

Animal	Route	Duration	NOAEL mg/kg bw/day	LOAEL mg/kg bw/day	Doses mg/kg bw/day	Reference
Monkey	Gavage+ subcutaneo us injection	28 days	150 (po) + 0.5 (sc)		30,150,300 (po) + 0.1, 0.5, 1.0 (sc)	Heywood et al.,1978
Rat	Gavage	1 month	125	250	125, 250, 500	Ito et al.,1978
Rat	Oral feed	2 months	225		22.5, 112.5, 225	Nolen et al.,1975
Rat	Oral feed	90 days	50	250	50, 250	Oser et al.,1965
Rat	Oral feed	90 days	750 (*)		750	Ikawa et al.,1978
Rat	Oral feed	90 days	220		8.8, 44, 220	Kay et al.,1965
Rat	Oral feed	6 months	40	115	40,115,340, 1030	Yoneyama et al.,1972
Mouse	Drinking water	6 months		20 (**)	20	Watari et al.,1977
Rat	Oral feed	9 months	260	780	260, 780	Yoneyama et al.,1976
Rat	Drinking water	9 months	85	145	85, 145, 430	Yoneyama et al.,1976
Mouse	Oral feed	9 months	< 500	500	500, 1000	Yoneyama et al.,1976
Mouse	Drinking water	9 months	100	250	100, 250, 750	Yoneyama et al.,1976
Rat	Dermal	15 days	< 286	286	286, 427	Sadai et al.,1972

(*) the only dose tested
(**) effects disappeared during the course of the study

Data reproduced from http://www.heraproject.com/RiskAssessment.cfm

This table, reproduced from the risk assessment for the linear alkyl benzene sulfonates, shows the effect levels from the various oral toxicity studies cited in the risk assessment. Although not indicated in this table, the text of the risk assessment indicated effects in the liver and kidney from oral administration, including liver weight increase at 250 mg/kg/day (Oser et al., 1965), degeneration of renal tubules at 115 mg/kg/day (Yoneyama et al., 1972), enzyme changes of the liver and kidneys at 780 mg/kg/day (Yoneyama et al., 1976), increases in alkaline phosphatase, decreased glucose-6-phosphatase and glucose-6-phosphate dehydrogenase, increased isocitrate dehydrogeanse at 750 mg/kg/day (Ikawa et al., 1978), and hepatic damage at 20 mg/kg/day in

mice (Watari et al., 1977) (HERA 2004).

It should be noted also from these data that the NOAEL values vary widely, without an obvious explanation. It could be based upon the use of compounds of this class of varying chain lengths (as noted in the HERA assessment, "commercial LAS consists of more than 20 individual components") .

In vitro mutagenicity tests conducted with LAS (Ames Salmonella, recombination assay with *bacillus subtilis*, reverse mutation with *E. coli*) were negative, as were *in vivo* mutagenicity assays (chromosomal aberration test, dominant lethal assay, micronucleus assay).

A summary of developmental and reproductive toxicity studies for LAS was also presented in the HERA document and is shown below. These data show Maternal NOAEL values from oral studies ranging from 10 mg/kg/day in mice to 780 mg/kg/day in rat oral studies, with LOAELs ranging from 100 to 3330 mg/kg/day. There are no apparent developmental NOAELs that are below the maternal NOAELs, but only summary data are provided in the HERA assessment (2004). Oral NOAELs for teratogenicity ranged from 135 to 600 mg/kg/day, with a LOAEL of 600 mg/kg/day identified in one study. Dermal developmental maternal NOAELs range from 0.9 to 150 mg/kg/day, while maternal LOAELs range from 9 to 1500 mg/kg/day, possibly suggesting the LAS may be more toxic via the dermal route of exposure in some studies.

Table 24: Summary of the developmental and teratogenicity tests

Animal	**Route**	**Exposure in pregnancy**	**NOAEL maternal** mg/kg bw/day	**NOAEL Teratogenicity** mg/kg bw/day	**Dose** mg/kg bw/day	**Reference**
Rat	Drinking water	Day 6-15	383	383	383	Endo et al.,1980
Rat	Oral feed	Day 0-20	780	780	80, 780	Tiba et al.,1976
Rat	Oral feed	Day 6-15 + 60 days prior mating	225	225	22.5, 112.5, 225	Nolen et al.,1975
Rat	Gavage	Day 6-15	300	600	0.2, 2, 300, 600	Palmer-a et al.,1975
Mouse	Gavage	Day 7-13	40	400	4, 40, 400	Takahashi et al.,1975
Mouse	Gavage	Day 6-15	10	300	10, 100, 300	Shiobara et al.,1976
Mouse	Gavage	Day 6-15	(2)	300	0.2, 2, 300, 600	Palmer-a et al.,1975
Rabbit	Gavage	Day 2-16	135	135	22.5, 45 ,135	Nolen et al.,1975
Rabbit	Drinking water	Day 6-18	3330 (**LOAEL**)	3330 (**LOAEL**)	3030	Endo et al.,1980
Rat	Dermal	Day 2-15	6	60	0.6, 6, 60	Palmer-b et al.,1975
Rat	Dermal	Day 0-21	20	400	20, 100, 400	Daly et al.,1980
Mouse	Dermal	Day 0-13	110	110	110	Sato et al.,1972
Mouse	Dermal	Day 6-15	150	1500	15, 150, 1500	Imahori et al.,1976
Rabbit	Dermal	Day 1-16	0.9	90	0.9, 9, 90	Palmer-b e4t al.,1975
Mouse	SC	Day 0-3 or Day 8-11	20	200	20, 200	Takahashi et al., 1975

Alcohol Sulfates

With respect to the alcohol sulfates, from the summary of toxicity data in the HERA (2002) assessment, a similar low order of acute toxicity is observed as with the linear alkylbenzene sulfonates. Oral LD_{50} values are reported as ranging from 1.4 to > 8 g/kg. Acute dermal LD_{50} values were not available but testing up to 500 mg/kg did not cause mortality in rabbits. As with the linear alkylbenzene sulfonates, skin and eye irritation are observed with the alcohol sulfates at concentrations of 5-10% and above. No dermal sensitization is reported for this class of chemicals.

Toxic effects are observed from repeated dose administration of alcohol sulfates. These data are again reproduced from the HERA risk assessment below:

Table 4
Repeated dose toxicity profile following oral administration of AS (selected studies)

Surfactant	Species	Route	Exposure duration	Dose/ Concentration	NOEL/LOEL	Dose-dependent Target Organ Effects (males: m; females f)	References (App. III)
C_{12} AS Na	Rat	Oral (gavage)	28-days (29-day post exposure observation period)	0, 30, 100, 300, 600 mg/kg/day	NOEL= 100 mg/kg/day LOEL = 300 mg/kg/day	Forestomach (irritation, ulceration, partially reversible (both sexes). Organ weight/body weight increases: liver (f); kidneys (m); testes.	Henkel, 1987 (unpublished, TRS 16)
C_{12-14} AS TEA	Rat	Oral (gavage)	28-days	0, 70, 250, 750 mg/kg/day	NOEL= 70 mg/kg/day LOEL = 250 mg/kg/day	Forestomach (inflammation, edema and ulceration): reversible.	Henkel 1988 (unpublished TRS 15,)
C_{16-18} AS Na	Rat	Oral (gavage)	90-days (33-day post exposure observation period)	0, 100, 300, 900 mg/kg/day	NOEL= 100 mg/kg/day LOEL = 300 mg/kg/day	Some deaths at high dose. Forestomach (inflammation, ulceration, both sexes, partially reversible). Organ weight/body weight increases: liver (m, f). Organ weight-body weight decreases: thymus, adrenals (f); (reversible).	Henkel 1987 (unpublished, HESA 1)
C_{12} AS Na	Rat	Oral (dietary)	21-days	0, 0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1.5% in diet (0, 25, 52, 108, 208, 423, 830, 1643 mg/kg/day)	NOEL= 109 mg/kg/day LOEL = 208 mg/kg/day	Liver: hypertrophy, reduced cytoplasmic fat and glycogenic vacuolation (especially in f). Liver enzyme changes. Organ weight/body weight increases: liver (especially in f); kidneys (f); brain (f). Decreased weight gains (m). Depleted body fat.	Unilever, 1976 (unpublished study L35,)
C_{12} AS Na	Rat	Oral (dietary)	90-days	0, 0.07%, 0.14%, 0.28%, 0.56%, 1.13%, 2.25% in diet (0, 59, 116, 230, 470, 950, 1900 mg/kg/day)	NOEL= 116 mg/kg/day LOEL = 230 mg/kg/day	Liver: hypertrophy, reduced cytoplasmic fat and glycogenic vacuolation (especially in f); liver enzyme changes. Organ weight/body weight increases: liver (m, f), kidneys (f), adrenals (f); brain (m, f); testes. Decreased weight gains (m, f). Depleted body fat.	Unilever, 1977 (unpublished study, L 36)

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As for the linear alkylbenzene sulfonates, the alcohol sulfates also show effects on the liver from repeated dose toxicity studies at doses which could be considered for setting toxicity endpoints of concern. There is less variation in NOAEL values compared to the linear alkylbenzene sulfonates but consistent effects on the liver are noted.

With regard to developmental and reproductive toxicity of alcohol sulfates, only one reproductive toxicity study was available for what is claimed to be a structurally-related compound, alpha olefin sulfonate. The summary of this study indicates no significant treatment-related effects up to 250 mg/kg/day in a 2-generation study. One published developmental toxicity study was available for alcohol sulfate which was tested up to 600 mg/kg/day by oral gavage in rats, mice, and rabbits (Palmer et al., 1975, in http://www.heraproject.com/RiskAssessment.cfm) and which reported a maternal NOAEL of 2 mg/kg/day for all species and developmental NOAELs of 300 mg/kg/day in rabbits and mice and 600 mg/kg/day in rats.

With respect to mutagenicity, data on *in vitro* and *in vivo* mutagenicity tests were summarized in an Appendix to the HERA document. As the data are extensive, they are not reproduced here. However, in summary, it is noted that most of the studies show negative results. There are some data indicating a positive response, for example, in an *in vivo* chromosome aberration test in hamsters, a dose of 2.5 g/kg showed marginal but statistically significant increases in chromatid gaps in high dose females. In a rodent dominant lethal assay at doses of 210/300, 960/980, and 3050/3010 mg/kg/day, decreased pregnancy frequency and increased early embryonic deaths were observed at week four of an 8-week study, although the dose causing this effect was not noted in the summary. The nature of the positive response may be based upon a non-specific disruption of cell membranes by a high concentration of the surfactant and not a specific mechanism.

Conclusions

The data cited by the Registrant in support of characterizing the toxicity of sulfonated oleic acid raises several issues with respect to the risk from exposure to sulfonated oleic acid:

1) The position by the Registrant that sulfonated oleic acid is biotransformed (metabolized and excreted) in a manner similar to the alcohol sulfates and/or linear alkylbenzene sulfonates is not supported by actual data but only by modeling results. An actual metabolism study would be helpful in addressing this issue.

2) The observation of liver and kidney toxicity from administration of the alcohol sulfates and the linear alkylbenzene sulfonates, as shown in the summary tables included in this memorandum, raises questions regarding the potential for sulfonated oleic acid to produce similar effects. In addition, the range of NOAEL values observed for both the results of testing of both classes of chemicals makes it difficult to compare results for a single chemical entity (i.e. sulfonated oleic acid) with chemical classes composed of more than one component. In order to determine whether there is any similarity, some side-by-side toxicity comparisons would need to be conducted with sulfonated oleic acid and the linear alkylbenzene sulfonates and alcohol sulfates to conclude with

any certainty that data can be bridged from the alcohol sulfates and/or linear alkylbenzene sulfonates. A minimum data set of one oral 90-day rodent study and an oral developmental study, in addition to the mutagenicity battery (bacterial reverse mutation assay, in vitro mammalian gene mutation assay and in vivo cytogenetics study) are required to determine if bridging is feasible.

Alternately, toxicology data on sulfonated oleic acid could be developed to meet the data requirements in support of the registered uses as a food-contact sanitizer. This would include (in addition to the acute toxicity data and standard mutagenicity battery) a developmental toxicity study in the rat, a 2-generation reproduction toxicity study in the rat, and subchronic toxicity studies in the rodent and non-rodent to support the indirect food uses for this active ingredient.

3) As with the repeated dose toxicity data, the available data on developmental toxicity and reproductive toxicity show NOAELs over a range of doses but no actual data on sulfonated oleic acid for comparison. Thus, a determination of an FQPA safety assessment, as needed for the indirect food uses of sulfonated oleic acid, could only be addressed through generation of data relevant for bridging as noted above or generation of data specific to sulfonated oleic acid to fulfill data requirements for the uses being supported in the RED.

References:

Human and Environmental Risk Assessment (HERA). 2004. Linear Alkylbenzene Sulphonate (CAS No. 68411-30-3). May 2004. http://www.heraproject.com/RiskAssessment.cfm

Human and Environmental Risk Assessment (HERA). 2002. Human and Environmental Risk Assessment on the ingredients of European household cleaning products. Alcohol Sulphates Human Health Risk Assessment. Draft. December 2002. http://www.heraproject.com/RiskAssessment.cfm

JohnsonDiversey 2004. Memorandum from F. Heitfeld to L. Amadio. Toxicity Review of Sulfonated Oleic Acid, Sodium Salt. September 2, 2004.